IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Michael Seitz et al. Art Unit 1611
Serial No. 10/728,654
Filed December 5, 2003
Confirmation No. 8454
For MICROCAPSULES WITH AMINE ADJUSTED RELEASE RATES
Examiner Barbara S. Frazier

Declaration of David Z. Becher under 35 C.F.R. §1.132

I, David Z. Becher, declare and state as follows:

(1) I am a Senior Research Specialist for Monsanto Technology LLC. I have been a formulator for Monsanto since 1979. My responsibilities for Monsanto include the development of glyphosate (Roundup®) formulations and, relevant to the present application, the development of slow release technologies, in particular the development of herbicidal compositions comprising microencapsulated herbicidal actives. I have experience in the development of slow release, microencapsulation technologies since 1980. Finally, I am a co-author of "Microencapsulation Technology and Future Trends" published in Pesticide Formulation and Adjuvant Technology, edited by Chester Foy and David Pritchard, CRC Press, 1996.

(2) I have been asked to review and have reviewed the non-final Office Action dated April 16, 2010 issued in connection with the present application. I have further reviewed the specification and claims of the pending application. I have reviewed the Office's bases for asserting that the claims are not enabled in view of the specification. I have reviewed the

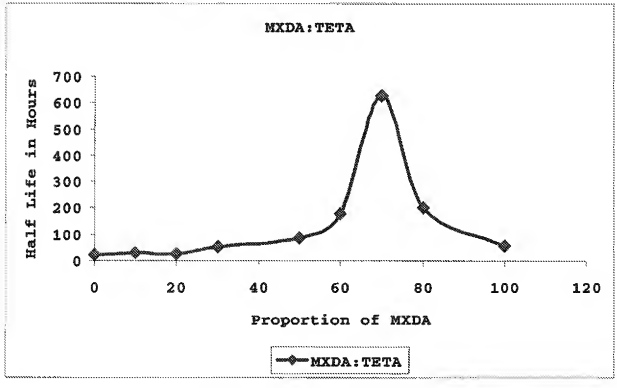
Office's bases for concluding that the claims are non-obvious and the disclosures of the cited Seitz et al. (U.S. 5,925,595) and Becher et al. (U.S. 4,563,212).

(3) It is my view that the specification and the examples provide sufficient guidance to enable the ordinarily skilled person to select principal and auxiliary amines in order to prepare microcapsules having a half life within the range of 5 to 100 days. The disclosure of the present application is a significant achievement in reducing unpredictability in the art of encapsulating materials by showing that the half life of release of microcapsules can be finely tuned by varying the ratio of amines used to prepare the polyurea shellwall.

(4) The specification and the examples provide a predictable and reliable method for selecting principal and auxiliary amines in order to prepare microcapsules having half lives within the claimed range. Examples 3A through 3I describe preparation of a series of microcapsules prepared using a blend of amines in varying amine ratios. The amine component comprised a blend of triethylene tetraamine ("TETA") and meta-xylene diamine ("MXDA"). In the context of the claims, this embodiment encompasses an auxiliary amine having an aryl moiety in combination with a principal amine comprising a linear polyalkylamine. The following table shows the relative proportions of the amines and the half lives of the resultant microcapsules prepared according to the methods described in these Examples:

Example	MXDA	TETA	Half Life in Hours	Half Life in Days
3I	100	0	57.84	2.41
3F	80	20	199.92	8.33
3E	70	30	626.4	26.1
3G	60	40	178.08	7.42
3D	50	50	88.8	3.7
3C	30	70	53.76	2.24
3B	20	80	25.92	1.08
3A	10	90	30	1.25
3H	0	100	24	1.00

(5) Below is a graphical depiction of the half-lives (in hours) as a function of the proportion of MXDA amine:



(6) In this embodiment, the half life of release appears to be strongly correlated to and thus predictable from the relative proportions of amine. The graph shows a trend that provides the ordinarily skilled person with the means to predict how varying the amine ratio affects the half life of release. Since the curve follows a substantially normal distribution, the

ordinarily skilled person would be able to reliably predict that microcapsules prepared using a ratio of MXDA:TETA that is intermediate the ratios of any two contiguous data points would have a half life of release falling substantially on the normal distribution curve.

(7) The specification contains additional Examples of microcapsules prepared using a blend of amines. Certain of these examples have a half life of release falling within the claimed range of 5 to 100 days. Importantly, certain of these Examples, like Example 3, also disclose consistent trends that provide the ordinarily skilled person with ability to predict the effect of varying the types of amines and the amine ratios on half life of release. Example 1 discloses microcapsules in which the polyurea shell wall is prepared using a blend of Jeffamine EDR148 and Jeffamine T403 in ratios of 60:40, 40:60, and 20:80. FIG. 1B shows a clear relationship between half life of release and the %equivalent of Jeffamine T-403 used in the amine blend. Example 4 discloses microcapsules in which the polyurea shell wall is prepared using a blend of Jeffamine T403 and TETA in a ratio of 0:100 (Example 4A), 90:10 (Example 4B), and 50:50 (Example 4C). In the context of the claims, this embodiment encompasses an auxiliary amine comprising an epoxy-amine adduct in combination with a principal amine comprising a linear polyalkylamine. As shown in FIGS. 4A and 4B, the microcapsules of Examples 4B and 4C, prepared using the amine blend, exhibited superior control against wheat, wild oat, and green foxtail compared to the microcapsules of Example 4A, which were prepared using one amine. Example 6 discloses microcapsules in which the polyurea shell wall is prepared using a blend of TETA and an epoxyamine adduct prepared by reacting

TETA with diglycidyl ether of bisphenol A. The TETA was added in excess in each of Examples 6A, 6B, and 6C. The amines of some of the TETA reacted with the diglycidyl ether of bisphenol A to form the epoxy-amine adduct. Since excess TETA remained in reaction solution, the amine blend comprised the product epoxy-amine adduct and TETA. In the context of the claims, this embodiment encompasses an auxiliary amine comprising an epoxy-amine adduct in combination with a principal amine comprising a linear polyalkylamine. The specification provides guidance at paragraph [0236] that epoxy-amine adducts prepared from diglycidyl ether of bisphenol A increase release rates while epoxy-amine adducts prepared from phenolic resins decrease release rates. The microcapsules of Example 6A were prepared using a 18:82 epoxy:TETA ratio, and the half-life of 15.7 days. The microcapsules of Example 6B were prepared using a 33.3:66.7 epoxy:TETA ratio, and the half-life was 9.5 days. The microcapsules of Example 6C were prepared using a 46:54 epoxy:TETA ratio, and the half-life was 5.8 days. The specification thus contains multiple examples of microcapsules having half lives within the claimed range. Examples 1, 3, and 6 additionally disclose trends that the ordinarily skilled person could use to determine appropriate amines for preparing microcapsules and appropriate amine ratios to reach desired half lives of release.

(8) In view of the multiple examples describing microcapsules having half lives of release within the claimed range and the examples showing trend data, the amount of experimentation the ordinarily skilled person must conduct in order to prepare microcapsules having half lives within the claimed range is not excessive. Additionally, the type of

experimentation is routine in the field of encapsulating materials. The specification describes at Example 1D paragraph [0170] in sufficient detail the test for determining the half life of a population of microcapsules. The ordinarily skilled person thus does not have to do any substantial experimentation in order to determine if a population of microcapsules has a half life within the claimed range since the half life determination test is provided. A technician having an associate's degree or a sound high school education would be capable of carrying out the half life determination technique. I would also characterize the type of experimentation necessary to determine if other amine blends yield microcapsules having half lives within the claimed range as routine. The specification provides multiple examples of microcapsules having half lives within the claimed range. The specification provides multiple examples of the types of amines that can be used in a two amine blend in order to prepare microcapsules having half lives within the claimed range. The specification provides trend data showing how half life of release can be varied by the ratio of amines. Based on the variety of amines used in the examples, the ordinarily skilled person can easily predict if amines having somewhat different but closely related structures are potentially useful in preparing microcapsules having half lives within the claimed range. The ordinarily skilled person can, through routine experimentation, easily prepare a series of microcapsules having varying ratios of two amines, like the series shown in Examples 3A through 3I in Table 1. The ordinarily skilled person can easily determine, through routine experimentation, if a series of amine ratios will show the type of strong correlation between amine ratio and half life like the series of microcapsules of Examples 3A through 3I.

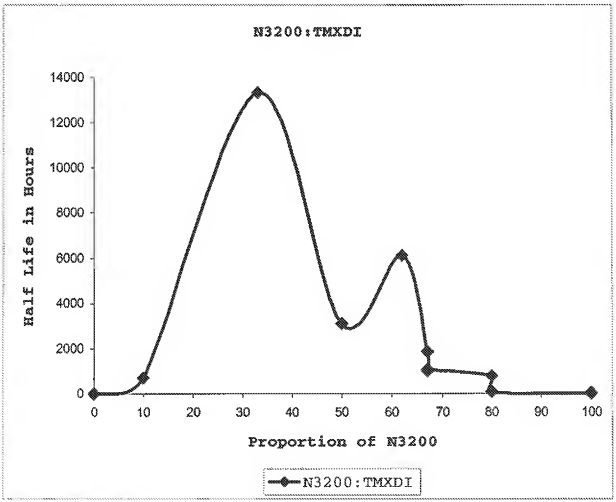
(9) The Office Action states "The relative skill of those in the art is high, that of a PhD." I agree that there are certainly researchers in the field of encapsulating materials with polymeric shellwall materials that are highly skilled. However, the amount of skill necessary to prepare microcapsules within the boundaries of the claims is not necessarily someone with a PhD. In view of the extensive guidance provided by the specification and working examples, the specific examples of amines used to prepare microcapsules meeting all of the claim limitations, and the trend data, a person having lower skill in the art could readily prepare microcapsules within the scope of the claims.

(10) The state of the art was unpredictable before the discovery and disclosure of the subject matter of the present application. The cited Seitz et al. application illustrates the highly unpredictable nature of the art. Seitz et al. disclose the use of and manipulation of a pair of isocyanates for the preparation of controlled release microcapsules. Seitz et al. prepared microcapsules using a blend of the polyisocyanates Desmodur N3200 ("N3200" in Tables 1 and 2) and meta-tetramethylxylylene ("TMXDI" in Tables 1 and 2) in varying proportions. The microcapsules of Examples 1-6 and 13-18 were prepared using triethylene tetraamine ("TETA" in Table 1). The following table shows the relative proportions of polyisocyanate and the half lives of the resultant microcapsules prepared according to the methods described in these Examples:

Example	N3200	TMXDI	Half Life in Hours	Half Life in Days
5	100	0	26	1.0833
15	100	0	4	0.166
14	80	20	72	3

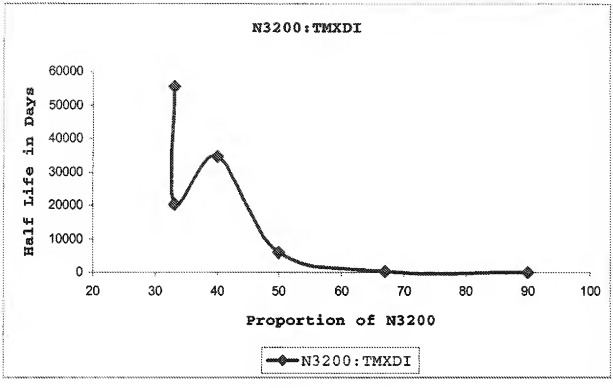
17	80	20	816	34
1	67	33	1080	45
13	67	33	1008	42
16	67	33	1848	77
18	62	38	6096	254
2	50	50	3120	130
3	33	67	13320	555
4	10	90	696	29
6	0	100	20	0.8333

(11) Below is a graphical depiction of these half-lives (in hours) as a function of the proportion of N3200 polyisocyanate:



(12) The microcapsules of Seitz et al.'s Examples 7-12 were prepared using the same blend of polyisocyanates with triethylene tetraamine ("DETA" in Table 1) instead of TETA. All

of the half lives were very long, except for Example 11, which had a half life of three days. Below is a graphical depiction of the half-lives (in days) as a function of the proportion of N3200 polyisocyanate:



(13) In each graph of the Seitz et al. data, the relationship between proportions of isocyanate monomers and half life is erratic, volatile, and unreliable. The lines connecting the points on each graph show that the distribution of half lives is not a normal distribution. Thus, the lines do not define any sort of clear correlation between two contiguous points or among the entire set of data points on the graph. The ordinarily skilled person would not be able to predict that microcapsules prepared using a ratio of isocyanates intermediate the ratios of two contiguous data points would have a half life of release intermediate the two contiguous data points. The erratic nature of the data precludes such predictability.

(14) Seitz et al. nominate five variables as affecting release rates: (1) permeability of the shell wall as controlled by the ratio of isocyanates at Col. 4, line 64 to Col. 5, line 12, (2) wall thickness at Col. 1, lines 53-62, (3) nature of the active, or mixture thereof with, e.g., a safener at Col. 4, lines 21-32, (4) selection of solvent at Col. 5, lines 29-37, and (5) temperature at Col. 20, lines 1-17. All these variables have been nominated by Seitz et al. as affecting the permeability of the shell wall. No such significance is placed on the amines, and no suggestion is made that a blend of amines may be useful for predictably controlling the half life of microcapsules by varying the principal to auxiliary amine ratio and thereby avoiding the effect of the erratic, volatile, and unreliable relationship between the isocyanate ratio and the half life of release. Rather, Seitz et al. merely recognized that all the amines that were listed in their disclosure have the same function, which was to react with the isocyanate functionality present on the isocyanate molecules. Seitz et al. further enabled the ordinarily skilled person to predict that each of these individual amines would function adequately. However, Seitz et al.'s disclosure and data would not have made it predictable that the use of a primary amine and an auxiliary amine at varying ratios would provide superior control of the release rate. In contrast to the graphical presentations of the Seitz et al. data, the half life release values for the formulations of the present invention are smoothly and reliably correlated to the relative proportions of principal and auxiliary amines, and the half lives fall in a useful range over wide ranges of relative proportions, as shown in the chart on page 29 and the graph on page 30 in the Response to the August

27, 2009 Final Office Action. In reviewing the various graphical presentations of data in that Response, it is critical to note that the half lives are given in hours and the scale extends to just 700 hours in the graph plotting the applicants' compositions on page 30, while the scale extends to 60,000 *days* in the graph plotting Seitz et al.'s compositions on page 28. 60,000 days is 1,440,000 hours. Accordingly, the scale of the graph on page 28 is over 2000x the scale of the graph on page 30. The scale of the graph on page 27 is to 14,000 hours, which is still 20x the scale of the graph on page 30.

(15) It is important to keep these differences in scale in mind if one is to compare the Seitz et al. data with the half lives of release obtained from the microcapsules of the present application, which were prepared using a blend of a principal amine and an auxiliary amine. The data are directly comparable since the difference between the half lives and their reproducibility result basing half life control on a combination of different polyisocyanates rather than a combination of different polyamines. A comparison of these data yields the following conclusions, among others, regarding the exceedingly and unexpectedly superior control of half life of release obtained by using a blend of amines over a blend of polyisocyanates:

(16) First, the half lives of release of the Seitz et al. examples vary widely with relatively minor changes in the relative proportions of the polyisocyanates. Compare this to the half lives of release of the present application's examples, which show a consistent relationship to composition and avoid the drastic sensitivity to small increments of change in

relative proportions that characterize the polyisocyanates. Nothing in Seitz et al.'s disclosure would have given the ordinarily skilled person the ability to predict that the half life of release could be so reliably controlled by varying the relative proportion of the amines in a polyamine blend. This is thus one unexpected benefit of using a principal amine and an auxiliary amine to prepare the microcapsule shell wall.

(17) Second, many of the half lives of release of the Seitz et al. examples are excessively long and thereby result in commercially impractical pesticidal materials. Some of the examples had measured half lives on the order of *years* (e.g., 16 years, 56 years, and even 95 years for Seitz et al.'s examples 8-10).[1] The data show that only minor variations in the relative ratio of polyisocyanates can alter the release rate characteristics widely from short half lives to exceedingly long half lives. Only a select window of polyisocyanate proportions yields microcapsule release rates of commercially acceptable durations using Seitz et al.'s method. Given the steep rate of change in half life versus isocyanate ratio, one skilled in the art would have very little confidence that the acceptable window would be reproducible. In the present application, the entire range of polyamine blends yield commercially useful microcapsule release rates. For example, over the entire range of relative proportions of amines, the half life varies from about 1 day to about 26 days. Significantly, modest variation in amine ratio does not throw the release rate out of control. Depending upon

[1] While some of these half-lives were extrapolated out to very long durations and thus may involve some experimental or theoretical error in their measurement and calculation, particularly since it is impossible to measure a half live of 95 years in a practical manner, nevertheless, it is safe to conclude that the half-lives of certain of the Seitz et al. microcapsules are far longer than a half life that is commercially useful.

soil conditions, climate, the crop, the types of weeds that may be present, etc., a commercial use may be found for each and every example of the inventive pesticidal material. This contrasts sharply with Seitz et al., whose examples show only a few of the microcapsules (e.g., some of the microcapsules having less than 10% N3200 or greater than 80% N3200) have half lives of comparable duration, and the extreme sensitivity of half life to small changes in proportions makes quality control difficult, if not impossible. Nothing in Seitz et al.'s disclosure would have given the ordinarily skilled person the ability to predict that the entire range of relative proportions of the amines in a polyamine blend yield commercially viable pesticidal materials while only select, narrow and potentially unstable windows of proportions of isocyanates result in commercially viable controlled release materials using the Seitz et al. method. Therefore, this is another unexpected benefit of using a principal amine and an auxiliary amine to prepare the microcapsule shell wall.

(18) The cited Becher et al. reference contains a claim requiring the use of two amines. This appears to be the extent of any disclosure of two amine blends. The reference does not contain any examples of microcapsules using two amines. The reference does not suggest combinations of classes of amines and thus does not disclose the various combinations required by the claims. This reference does not provide any half life data whatsoever, much less the half life of microcapsules prepared using a blend of amines within the classes required by the claims.

(19) In view of the unpredictable nature of the Seitz et al.'s microcapsules and the lack of half life data in Becher et al.'s disclosure, it is my view that the ordinarily skilled person would not have been able to predict that the use of amine blends would have enabled the preparation of microcapsules having finely tunable half lives of release within the claimed range. The discovery of such a robust relationship between amine ratio and half life is therefore a significant contribution toward eliminating much of the unpredictability in this field that existed before the disclosure of the present application.

(20) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

David Z. Becher

David Z. Becher

Oct 4, 2010

Date